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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/829,505	04/22/2004	Shan X. Wang	STAN-571 (S00-163)	6970

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Stanford University Office of Technology Licensing
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EXAMINER	
DO, PENSEE T	

ART UNIT	PAPER NUMBER
1641	

MAIL DATE	DELIVERY MODE
08/03/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/829,505	WANG ET AL.	
	Examiner	Art Unit	
	Pensee T. Do	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) _____ is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Priority

This application 10829505, with PG Pub. No. 20050100930 filed 04/22/2004, claims Priority from Provisional Application 60519378, filed 11/12/2003.

Prosecution Re-opened

The finality is withdrawn herein since the applicants' argument is found persuasive.

After-Final Amendment Entry & Claims Status

The amendment filed on April 19, 2010 has been acknowledged and entered.

Claims 1-17, 19 and 48 are being examined.

Claims 20-47 are withdrawn.

Claimed Invention

1. (Currently Amended) A method of detecting a complex, the method comprising:

providing a first molecule bonded to at least one magnetizable nanoparticle;

providing a second molecule bonded to a substrate;

contacting the first molecule to the second molecule under conditions suitable for selective binding of the first molecule to the second molecule to form a complex; and

detecting the complex, wherein said detecting comprises applying a DC bias field and an AC tickling field.

Withdrawn Rejections

Rejections under 103 in the previous office action are withdrawn herein.

New Grounds of Rejection

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-8, 10, 11, 17, 19 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fox (WO 01/14591, published March 1, 2001) in view of Besse et al. (Applied Physics Letters, Volume 80, no. 22, 3 June 2002, pp. 3199-4201).

Fox teaches a method of detecting a molecule of interest, the method comprises providing a first molecule bonded to a magnetizable nanoparticle; providing a second molecule bonded to a substrate; contacting the first molecule with the second molecule to promote binding between the two molecules to form a complex; detecting the complex. (see pg. 20, lines 15-18; pg. 6, lines 15-20).

However, Fox fails to teach that said detecting comprises applying a DC bias field and an AC tickling field.

Besse teaches detection and characterization of a single magnetic bead using silicon Hall sensor. The method of detection is applying a DC bias field perpendicular to

the sensor and an AC field in either z (H2) direction or x direction (H1). Besse teaches that applying a dc field and an AC field orthogonally to the DC field increase the change in magnetic induction. Such method also can be applied to an array of sensors and requires low ac magnetic field. Besse also teaches that the beads are covered with different chemical coatings and can be specifically attached to the desired targets such as cells, nucleic acids, bacteria etc. and is used for isolation of tumor cells and DNA sequencing and detecting the presence of the bead attached on a surface (see figure 1; entire document especially pg. 4200).

Therefore, it would have been obvious to one of ordinary skills in the art to apply the concept of using DC current and AC current (low frequency AC tickling field) in a Hall Sensor to detect magnetic response of a magnetic bead as taught by Besse to the method of Fox to detect predetermined region of a magnetic marker or particles in assay because using such combination of Dc and Ac magnetic fields increase the change in magnetic induction and such method can be used to an array of sensors and requires low ac magnetic field. (see Besse, pg. 4200). One of ordinary skill in the art would have a reasonable expectation of success in combining these teachings because they both teach using magnetic beads for isolation of cells and DNA sequencing and detecting the presence of the magnetic bead attached on a surface.

For claims 2-8, Fox teaches that the target molecule/specific binding molecule (first molecule or second molecule respectively) are among proteins (antigens/antibodies), polypeptides, nucleic acids (see pg. 11, lines 14-15; pg. 20, lines 14-15; pg. 21, lines 6-7).

For claims 10-11, Fox teaches that the magnetic particles are ferromagnetic, ferrimagnetic, paramagnetic or superparamagnetic. (see pg. 8, lines 20-23).

For claims 17 and 19, Fox teaches using a sensitive giant magnetoresistive ratio sensor (GMR) to detect the complex. The GMR sensor advantageously includes biasing magnets for producing an applied biasing magnetic field. The input voltage and the output sensor are routed to an operational amplifier and the output signal (net signal) is measured. This output signal will vary with the intensity of the an extemally applied magnetic field. (see pg. 13, line 25-pg. 14, line 10).

For claim 48, Besse teaches that the AC field is applied orthogonally to the DC bias field. (see Besse p. 4200, col. 2, 2nd paragraph; figure 1).

Claims 1-8, 10, 11, 14-17, 19 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coehoorn et al. (WO 03/054523, published July 3, 2003) in view of Besse et al. (Applied Physics Letters, Volume 80, no. 22, 3 June 2002, pp. 3199-4201).

Coehoorn teaches a method of magnetic detection comprising providing biological molecules on a substrate of a magnetoresistive device; adding magnetic nanoparticles conjugated with binding molecules specific for the biological molecules on the substrate of the magnetoresistive device so that the biological molecules on the substrate and the nanoparticles form a complex; detecting such complex. (see abstract; pg. 5, lines 18-30).

However, Coehoorn fails to teach said detecting comprises applying a DC bias field and an AC tickling field.

Besse teaches detection and characterization of a single magnetic bead using silicon Hall sensor. The method of detection is applying a DC bias field perpendicular to the sensor and an AC field in either z (H2) direction or x direction (H1). Besse teaches that applying a dc field and an AC field orthogonally to the DC field increase the change in magnetic induction. Such method also can be applied to an array of sensors and requires low ac magnetic field. Besse also teaches that the beads are covered with different chemical coatings and can be specifically attached to the desired targets such as cells, nucleic acids, bacteria etc. and is used for isolation of tumor cells and DNA sequencing and detecting the presence of the bead attached on a surface (see figure 1; entire document especially pg. 4200).

Therefore, it would have been obvious to one of ordinary skills in the art to apply the concept of using DC current and AC current (low frequency AC tickling field) in a Hall Sensor to detect magnetic response of a magnetic bead as taught by Besse as a magnetic detection sensor in the method of Coehoorn to detect predetermined region of a magnetic marker or particles in assay instead of using the magnetoresistive sensor of Coehoorn, which requires complicated and costly technologies as mentioned by Besse (see pg. 4199, first col.), because using such combination of Dc and Ac magnetic fields increase the change in magnetic induction and such method can be used to an array of sensors and requires low ac magnetic field. (see Besse, pg. 4200). One of ordinary skill in the art would have a reasonable expectation of success in combining

these teachings because they both teach using magnetic beads for isolation of cells and DNA sequencing and detecting the presence of the magnetic bead attached on a surface.

For claims 2-8, Coehoorn teaches the molecules are DNA, RNA, proteins (antigens or antibodies), or peptides, etc. (see pg. 8, lines 3-20).

For claims 10 and 11, Coehoorn teaches that the magnetic nanoparticles are superparamagnetic. (see pg. 5, lines 28-36).

For claims 14 and 15, Coehoorn teaches that the magnetic nanoparticles diameter range between and 250 nm, preferably between 3 and 100 nm, or 10 and 60 nm. (see pg. 5, lines 28-36).

For claim 16, Coehoorn teaches using a spin-valve substrate. (see table on pg. 23).

For claims 17 and 19, Coehoorn teaches an external magnetic field is applied and a net signal generated by the magnetic field in the plane of the GMR elements is detected. (see pg. 11, lines 17-19; pg. 11, lines 28-33).

For claim 48, Besse teaches that the AC field is applied orthogonally to the DC bias field. (see Besse p. 4200, col. 2, 2nd paragraph; figure 1).

Claims 1, 2-8, 10, 11, 17, 19 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baselt (US 5,981,297, Nov. 9, 1999) in view of Besse et al. (Applied Physics Letters, Volume 80, no. 22, 3 June 2002, pp. 3199-4201).

Baselt teaches a method for detecting target molecules. The method comprises providing a recognition molecules bound to a surface of a magnetic field sensor; adding target molecules bound to magnetic particles; exposing the magnetic particles bound target molecules to the surface of the magnetic field sensor bound recognition molecules so that the molecules form a complex; detecting such complex. (see col. 3, lines 39-59).

However, Baselt fails to teach said detecting comprises applying a DC bias field and an AC tickling field.

Besse teaches detection and characterization of a single magnetic bead using silicon Hall sensor. The method of detection is applying a DC bias field perpendicular to the sensor and an AC field in either z (H2) direction or x direction (H1). Besse teaches that applying a dc field and an AC field orthogonally to the DC field increase the change in magnetic induction. Such method also can be applied to an array of sensors and requires low ac magnetic field. Besse also teaches that the beads are covered with different chemical coatings and can be specifically attached to the desired targets such as cells, nucleic acids, bacteria etc. and is used for isolation of tumor cells and DNA sequencing and detecting the presence of the bead attached on a surface (see figure 1; entire document especially pg. 4200).

Therefore, it would have been obvious to one of ordinary skills in the art to apply the concept of using DC current and AC current (low frequency AC tickling field) in a Hall Sensor to detect magnetic response of a magnetic bead as taught by Besse to the

method of Baselt to detect predetermined region of a magnetic marker or particles in assay because using such combination of Dc and Ac magnetic fields increase the change in magnetic induction and such method can be used to an array of sensors and requires low ac magnetic field. (see Besse, pg. 4200). One of ordinary skill in the art would have a reasonable expectation of success in combining these teachings because they both teach using magnetic beads for isolation of cells and DNA sequencing and detecting the presence of the magnetic bead attached on a surface.

For claims 2-8, Baselt teaches that the recognition molecules or the target molecules are peptides, antibodies, DNA or RNA, proteins, etc. (see col. 4, lines 3-7).

For claims 10 and 11, Baselt teaches that the magnetic particles are superparamagnetic (see col. 3, lines 60-65).

For claim 17, Baselt teaches applying an external magnetic field to detect the complex. (see col. 7, lines 25-30).

For claim 19, Baselt teaches detecting a net signal or resistance change in the magnetoresistive element. (see col. 8, lines 8-24).

For claim 48, Besse teaches that the AC field is applied orthogonally to the DC bias field. (see Besse p. 4200, col. 2, 2nd paragraph; figure 1).

Claims 1-8, 10, 11, 14, 15 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Terstappen et al. (US 6,623,983, September 23, 2003) in view of Besse et al. (Applied Physics Letters, Volume 80, no. 22, 3 June 2002, pp. 3199-4201).

Terstappen teaches a method for immobilizing magnetically labeled particulate entities on a collection surface via binding between specific binding pair members. The method comprises providing one member of a specific binding pair bound to the collection surface and the other member bound to magnetic nanoparticles; exposing the magnetic nanoparticles bound binding member to the collection surface to form a complex between the binding members; detecting said complex. (see col. 6, lines 18-50;col. 12, lines 53-57).

However, Terstappen fails to teach said detecting comprises applying a DC bias field and an AC tickling field.

Besse teaches detection and characterization of a single magnetic bead using silicon Hall sensor. The method of detection is applying a DC bias field perpendicular to the sensor and an AC field in either z (H2) direction or x direction (H1). Besse teaches that applying a dc field and an AC field orthogonally to the DC field increase the change in magnetic induction. Such method also can be applied to an array of sensors and requires low ac magnetic field. Besse also teaches that the beads are covered with different chemical coatings and can be specifically attached to the desired targets such as cells, nucleic acids, bacteria etc. and is used for isolation of tumor cells and DNA sequencing and detecting the presence of the bead attached on a surface (see figure 1; entire document especially pg. 4200).

Therefore, it would have been obvious to one of ordinary skills in the art to apply the concept of using DC current and AC current (low frequency AC tickling field) in a Hall Sensor to detect magnetic response of a magnetic bead as taught by Besse to the

method of Terstappen to detect predetermined region of a magnetic marker or particles in assay because using such combination of Dc and Ac magnetic fields increase the change in magnetic induction and such method can be used to an array of sensors and requires low ac magnetic field. (see Besse, pg. 4200). One of ordinary skill in the art would have a reasonable expectation of success in combining these teachings because they both teach using magnetic beads or isolation of cells and DNA sequencing and detecting the presence of the magnetic bead attached on a surface.

For claims 2-8, Terstappen teaches the binding members are proteins (antibodies, antigens, peptides,) or RNA or DNA. (see col. 8, lines 50-55; col. 9, lines 20-25; col. 10, lines 29-30).

For claims 10 and 11, Terstappen teaches that the magnetic nanoparticles are superparamagnetic. (see col. 2, lines 42-44).

For claims 14 and 15, Terstappen teaches the diameter of the magnetic nanoparticles range from 20-25 nm (see col. 2, line 53) or less than 200 nm. (see col. 9,line 64).

For claim 48, Besse teaches that the AC field is applied orthogonally to the DC bias field. (see Besse p. 4200, col. 2, 2nd paragraph; figure 1).

Claims 9, 12 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fox, or Baselt or Coehoorn in view of Besse as applied to claim 1, and further in view of Berning et al. (PGPub US 2005/0025969).

Fox, Baselt, Coehoorn and Besse have been discussed above.

However, they fail to teach that the first molecule is covalently bonded to at least one magnetizable nanoparticle by a gold-thiol linkage, and the nanoparticle comprises a noble metal surface layer such as a gold surface layer.

Berning teaches nanoparticles coated with a layer of gold including a magnetic nanoparticle central core, and a coating of gold completely encapsulating the magnetic nanoparticle central core. The composite further comprises thiol-bound functional group-containing spacer groups thereon the gold-coated magnetic nanoparticles. (see [0009]. The gold-coated magnetic nanoparticles are further coupled to recognition group such as proteins, peptides, nucleic acids, (see [0014]. The size of the magnetic nanoparticles range from 10 nm to 250 nm. (see [0011]).

It would have been obvious to one of ordinary skills in the art to use the magnetic nanoparticles coated with a gold surface layer and thiol group as taught by Berning the method of Fox, Baselt or Coehoorn modified by Besse because such gold-coated magnetic nanoparticles of Berning would prevent direct bio-contact to the magnetic material thus improving biocompatibility. A gold surface also allows good coupling through chemical attachment of binding agents or recognition agents such as peptides, proteins or nucleic acids. (see Berning [0010]).

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fox or Baselt in view of Besse as applied to claim 1, and further in view of Ferreira et al. (Journal of Applied Physics Vol. 93, No. 10, 15 May 2003, pp. 7281-7286 submitted by Applicants).

Fox, Baselt and Besse have been discussed above.

However, they fail to teach the substrate comprises a high sensitivity spin valve or a magnetic tunnel junction detector array.

Ferreira teaches using arrays spin valve sensors to detect magnetically labeled biomolecules. (See abstract, pg. 7282, col. 1, A).

Since Fox and Baselt teaches using GMR elements, it would have been obvious to one of ordinary skills in the art to use the spin valve element of GMR as taught by Ferreira to detect magnetic beads since spin valve-type GMR is a highly sensitive magnetic sensor element which exhibits a high-signal to noise ratio of output and stable operation.

Response to Arguments

Applicant's arguments with respect to claims 1-17 and 19 have been considered but are moot in view of the new ground(s) of rejection.

With regards to all of the 103 rejections, Applicants argue that one of ordinary skill in the art would have no objective reason to combine the secondary reference of Dames to any of the primary references in all the 103 rejections because Dames discloses that the interrogation process includes the step of subjecting the tag to a

magnetic field sufficient in field strength to saturate the high permeability magnetic material. Dames, Abstract; and col. 4, lines 5-15. In addition, Dames discloses that "When a tag containing a piece of high-permeability magnetic material is passed along the coils' axis through the region over which oscillation of the magnetic zero plane occurs, it will initially be completely saturated by the DC magnetic field." Dames, col. 7, lines 10-14. Thus, Dames discloses that the applied DC magnetic field completely saturates the magnetic tags.

Magnetic saturation occurs when an increase in an applied external magnetizing field cannot further increase the induced magnetization of a magnetic material, so the total induced magnetic field of the magnetic material reaches a maximum.[1] In addition, when a magnetic material is saturated, all of the magnetic domains within the magnetic material have magnetic moments that are aligned and parallel with the applied external field.[2]

As described above, in the method disclosed by Dames, the applied magnetic field completely saturates the magnetic tags. Thus, the total induced magnetic field of the magnetic tags is at a maximum, such that any increase in the applied external field will not further increase the induced magnetic field of the magnetic tags. In addition, because Dames discloses that the magnetic tags are completely saturated, all of the magnetic domains within the magnetic tags have magnetic moments that are aligned and parallel with the applied external field. As such, increasing the strength of the applied DC field or applying an additional AC field to the saturated magnetic tags will have no effect on the induced magnetic field of the saturated magnetic tags because

the induced magnetic field is already at a maximum. Moreover, applying an additional AC field to the saturated magnetic tags will not cause the magnetic moments of the

This is found persuasive and therefore all the 103 rejections in the previous office action are withdrawn.

However, a new reference, Besse, is applied to remedy for the missing elements, i.e. applying a DC magnetic field and an AC magnetic field to detect the presence of the magnetic beads.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Pensee T. Do whose telephone number is 571-272-0819. The examiner can normally be reached on Monday-Friday, 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Pensee T. Do/
Examiner, Art Unit 1641
/Jacob Cheu/
Primary Examiner, Art Unit 1641